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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,742	DOEKEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *error report*.

DETAILED ACTION

Status of the Application

Claims 1-26 are pending.

Applicant's amendment of claims 1-11, 13-25, addition of claim 26, and submission of a new sequence listing in paper and electronic form, in a communication filed on 1/9/2004, are acknowledged.

It is noted that the electronic form (CRF) of the sequence listing has not been entered as it contains errors. See attached raw sequence listing error report. Applicants are requested to correct the error in response to this Office Action. Applicants are advised to follow the instructions provided in the error report in regard to a new submission.

Applicants request reconsideration of the restriction requirement in regard to claims 14-25. Applicants submit that the stated basis for the distinctiveness between Group I and Group II is not entirely correct since the DNA fragments when inserted into a microorganism can be expressed and used in the method of Group I. Furthermore, Applicants argue that Group I and III do not relate to a DNA fragment coding for Asp-Phe but to DNA fragments encoding a non-ribosomal dipeptide synthetase. With regard to Groups II and III, Applicants submit that the assertion that the protein can be made by another process such as chemical synthesis is not deemed to be credible under the current state of the art.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement made by the previous Examiner of record. The method of Group I and the product of Group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the protein of Group III (dipeptide synthetase) can be used in the method of Group I as well as to raise antibodies. The method of Group I and the product of Group II are unrelated since the DNA of Group II is not made by the method

of Group I, nor it is required in the method of Group I. The method of Group I only requires the protein of Group III and not the DNA of Group II. The Examiner acknowledges that one could use the DNA of Group II to recombinantly make the protein of Group III in a microorganism, however it is noted that even if the method of Group I and the DNA of Group II were related as product and process of use, the DNA have other uses such as a hybridization probe, and the method of Group I could then be practiced with two different products. In regard to the DNA of Group II and the protein of Group III, each of these products comprise a chemically unrelated structure capable of separate manufacture, use and effect. The DNA of Group II comprises nucleotides, whereas the protein of Group III comprise amino acids. The DNA of Group II has other uses besides encoding the protein of Group III, such as a hybridization probe or in gene therapy. The protein of Group III can be used in materially different methods such as in making antibodies, as a therapeutic agent or in diagnostic methods (e.g. in screening). Furthermore, the protein of Group III can be prepared by processes which are materially different from recombinant expression of the DNA of Group II, such as by chemical synthesis, or by isolation and purification from natural sources. While the Examiner acknowledges that chemical synthesis of large proteins may not be the preferred method of synthesis, it is noted that chemical synthesis of proteins is yet another method of protein synthesis. Thus, for the reasons set forth above, the restriction requirement is deemed proper and is made FINAL.

Newly submitted claim 26 is deemed drawn to the elected invention and it will be examined herein. As indicated in previous Office Action Paper No. 11, mailed 9/9/2003, claims 14-25 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected without traverse in Paper No. 10, filed on 8/1/2003. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 1/9/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claims 1 and 26 are objected to due to the recitation of "wherein the N-terminal module of these minimal modules recognizes L-aspartic acid and the C-terminal module of these minimal modules recognizes L-phenylalanine and is covalently bound at its N-terminal end to the condensation domain". To clearly indicate the two limitations regarding the C-terminal module, it is suggested that the term be amended to recite "wherein the N-terminal module of these minimal modules recognizes L-aspartic acid, wherein the C-terminal module of these minimal modules recognizes L-phenylalanine and is covalently bound at its N-terminal end to the condensation domain". Appropriate correction is required.

3. Claims 2-13 are objected to due to the recitation of "Method for ...". For clarity and consistency with customary claim language, it is suggested that the term be replaced with "The method for....". Appropriate correction is required.

4. Claim 7 is objected to due to the recitation of "wherein glucose, L-Asp...". For clarity and consistency, it is suggested that the term be amended to recite "wherein the glucose, L-Asp...". Appropriate correction is required.

5. Claims 6-7 are objected to due to the recitation of "switched on". The term is colloquial speech and should be replaced with a term commonly used in the art such as "induced". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 5-13, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims as written require only two minimal modules which recognize both L-aspartic acid and phenylalanine but no requirement is recited in regard to a thioesterase releasing factor. The specification in page 6, lines 18-22, teaches that the dipeptide (condensation product) is covalently linked to the multi-enzyme complex (dipeptide synthetase) and that release of the dipeptide is required for synthesis of Asp-Phe. The instant claims do not include a step indicating the release of the dipeptide from the dipeptide synthetase complex. It is noted that adding limitations in claims 1 and 26 regarding the presence of a thioesterase domain in the dipeptide synthetase which would allow the release the dipeptide would obviate the rejection. Also, note that a limitation regarding a thioesterase Type II (claim 5 and claims 6-10 dependent thereon) is not sufficient since as known in the art and disclosed by Applicants in page 15, a thioesterase Type II is not involved in the release of the dipeptide. Correction is required.

8. Claim 2 is indefinite in the recitation of "wherein the condensation domain...is covalently bound to the module recognizing..." for the following reasons. Claim 1 recites "comprising two minimal modules connected by one condensation domain". The term "connected" implies a physical linkage such as that of a covalent bond. Therefore, as it is unclear how it further limits claim 1 since claim 1 appears to indicate that the L-Asp module is covalently linked to the condensation domain in view of the term "connected". It is suggested that if the modules and condensation domain are not intended to be all covalently linked, claim 1 be amended to recite, for example, "comprising two modules, a condensation domain and a thioesterase domain". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-13 remain rejected and newly added claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 11, mailed on 9/9/2003.

11. Applicants argue that the specification sets forth the functional and structural properties of non-ribosomal peptide synthetases by example and by general description. In particular, applicants argue that the specification provides detailed description of where the minimal modules can be found within the larger non-ribosomal peptide synthetase and that the mechanism of peptide synthesis is a co-linear synthesis mechanism. Applicants further argue that the specification teaches that the dipeptide synthetase must have a module which recognizes L-Asp and another module which recognizes L-Phe and that the genus of synthetases require only those modules which recognize L-Asp and L-Phe. Applicants argue that the table in page 9 disclose core motifs and consensus sequences for the adenylation, thiolation, condensation, and thioesterase domains. Applicants indicate that the instant case is not like the situation in University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WDNY 2003) since they have disclose in enough detail the claimed invention. Applicants argue that the present case should be governed by Amgen Inc. v. Hoechst Marion Roussel, Inc. 65 USPQ2d 1385 (Fed. Cir. 2003) since each of the types of functional domains required to practice the claimed method were known at the time of the invention and would not be easily misunderstood by ordinary skilled artisans. Applicants further refer to

the specification to indicate that information has been provided regarding the condensation domain, the thioesterase releasing factors and type II thioesterases.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1-13 or avoid the rejection of claim 26. Claims 1-13 are directed to a method to produce an Asp-Phe dipeptide with a genus of dipeptide synthetases, wherein the dipeptide synthetases comprise two minimal modules, wherein one of the modules recognizes L-Asp and the other recognizes L-Phe, wherein each of these modules comprise a genus of adenylation domains, and a genus of thiolation domains, and wherein the two modules are connected by a genus of condensation domains. Claim 26 is still drawn to a method to produce an Asp-Phe dipeptide with a dipeptide synthetase comprising a genus of condensation domains. The Examiner acknowledges the teachings of the specification, Table 1, the working example provided, the state of the art, the findings in University of Rochester v. G.D. Searle & Co, and Amgen Inc. v. Hoechst Marion Roussel, Inc. However, it is noted that the instant rejection has been applied in view of the lack of disclosure as to the structure of all the Asp/Phe adenylation, condensation, thiolation, and thioesterase domains from any non-ribosomal peptide synthetase encompassed by the claims. The consensus motifs disclosed in Table 1, while providing additional information regarding some of the structural elements in adenylation, thiolation, condensation, and thioesterase domains, do not provide any clue as to whether these motifs are all that is required in any polypeptide to display the required activity, i.e. adenylation, condensation, thiolation or thioesterase activity. In addition, the specification provides no clue as to whether these motifs are specific to Asp/Phe adenylation, thiolation, condensation or thioesterase domains or if they are found in any amino acid adenylation, thiolation, condensation or thioesterase domain.

While a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of species defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in

the instant case, (1) there are no recited structural features for the domains (polypeptides) required in the claims, and (2) the structural features described in Table 1 do not constitute a substantial portion of the genus of domains required since each of these structural features represent a minor portion of the structure of these domains and the remainder of their structure is completely undefined. Many structurally diverse domains are encompassed by the claims and while some peptide synthetases are known, the structural characteristics provided in the specification are not deemed sufficient to adequately describe a potentially large genus of polypeptides. Thus, one of skill in the art cannot reasonably conclude that the claimed invention is adequately described by the specification.

13. Claims 1-13 remain rejected and newly added claim 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for the production of Asp-Phe using a hybrid Asp-Phe dipeptide synthetase, wherein the dipeptide synthetase comprises two minimal modules and a thioesterase domain, wherein one of the minimal modules recognizes L-Asp and the other minimal module recognizes L-Phe, wherein the minimal modules are connected by a condensation domain, wherein the minimal module recognizing L-Phe is covalently bound at its N-terminal end to the condensation domain, wherein each of these minimal modules comprise an adenylation domain and a thiolation domain containing a 4'phosphopantetheinyl cofactor, and wherein the adenylation, thiolation, condensation and thioesterase domains are encoded by the srfB and the srfC genes from B. subtilis ATCC 21332 (encoding surfactin synthetase) and/or the tyc operon (encoding tyrocidine synthetase) from B. brevis ATCC 8185, and (2) the method of (1) wherein a thioesterase type II is also used in addition to the dipeptide synthetase, does not reasonably provide enablement for the method described above in (1) or (2) wherein the Asp-Phe hybrid dipeptide synthetase comprises any Asp/Phe adenylation, thiolation, condensation or thioesterase domain. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

14. Applicants argue that each of the components of the minimal modules are known in the art and those of skill in the art would be able to refer to the existing literature to find additional examples of each of the components required. Applicants indicate that structural homology is not at issue in regard to enablement and one of skill in the art would only need known existing adenylation domains, thiolation domains, condensation domains, thioesterase releasing factors and thioesterase Type II proteins for constructing the dipeptide synthetases. Applicants submit that one of skill in the art would recognize whether a particular module recognizes L-Asp or L-Phe or any other amino acid. Applicants have submitted two references, van Sinderen et al. (Mol Microbiology 8(5):833-841, 1993) and Konz et al. (Chemistry & Biology 6(2):R39-R48, 1999) in support of the argument that the amount of experimentation needed is routine given the teachings of the specification and the general skill in the art.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1-13 or avoid the rejection of claim 26. As discussed above, while the Examiner acknowledges the teachings of the specification and the state of the art, the specification provides no clue as to whether these motifs are specific to Asp/Phe adenylation, thiolation, condensation or thioesterase domains. Furthermore, there is no teaching as to whether these motifs is all that is required for any polypeptide to be an Asp/Phe adenylation, thiolation, condensation, or thioesterase domain. The Examiner disagrees with Applicant's contention that structural homology is not at issue in regard to enablement and that all that is required is known existing adenylation domains, thiolation domains, condensation domains, thioesterase releasing factors and thioesterase Type II proteins. The scope of the claims requires any Asp/Phe adenylation domain, thiolation domain, condensation domain, and thioesterase domain to practice the claimed method. As such, there is no limitation in regard to the use of known domains only. Unknown domains are also encompassed by these claims. In view of the scope of the claims, one of skill

in the art would have to know or have an idea as to how to practice the claimed method with domains which have not been disclosed in the art. Since the structure of some of these domains is known, one approach to isolate these unknown domains is to use structural homology with those domains already known. However, as indicated in the previous action, the state of the art teaches the unpredictability of isolating proteins of similar function using structural homology. In view of the lack of information as to how to practice the claimed invention with other domains, it will require undue experimentation to practice the full scope of the claimed method.

In regard to the teachings of van Sinderen et al. and Konz et al., while it is agreed that (1) there is a general consensus as to the general structure, domain organization and mode of operation of peptide synthetases, (2) some highly conserved motifs of the catalytic domains of peptide synthetases are known, and (3) the structure of other peptide synthetases is known, neither the specification nor the art provides any information as to which are the critical structural elements required in any polypeptide to be an Asp/Phe adenylation, thiolation, condensation, or thioesterase domain. Furthermore, the highly conserved motifs disclosed have not been shown to be either specific for Asp/Phe adenylation, thiolation, condensation, or thioesterase domains, nor have they been shown to be the only structural elements required to display the required functional characteristics. Since structure determines function and only small structural elements are known for the genus of domains encompassed by the claimed (i.e. consensus motifs), it is unclear as to how one of skill in the art can reasonably conclude that the specification or the art enables the full scope of the claims in view of the fact that a major part of the structures of these domains is unknown.

In addition to the lack of enablement as it relates to the adenylation, thiolation, condensation and thioesterase domains, already discussed, it is noted that claims 1 and 26 are also directed to a method for the production of Asp-Phe with a dipeptide synthetase which lacks a thioesterase domain (or thioesterase releasing factor). As indicated in Claim Rejection under 35 USC 112, second paragraph, the specification

teaches that a releasing factor is required to obtain the dipeptide formed. However, the specification does not teach how to practice the claimed invention in the absence of a thioesterase domain, i.e. no teaching as to how to obtain the dipeptide without the thioesterase domain/releasing factor. For the reasons set forth above, one cannot reasonably conclude that Applicant has provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

16. No claim is in condition for allowance.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 30, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1652